MERCK INSTITUTE
FOR
THERAPEUTIC RESEARCH
RAHWAY, N. J.

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Dr. J. Lederberg
Department of Genetics
University of Wisconsin
Madison 6, Wis.

Dear Doctor Lederberg:

Some weeks ago you sent me a set of reprints which I shall always cherish as an example of the confidence scientists place in the assumption that their publications are read. On page 128 of a paper called "Genetics of Resistance to Bacterial Inhibitors," you have a question written in the margin. The chances that I would ever read a paper with this title are so remote that I can only conclude that the Umbreit luck is still holding, inasmuch as out of the group I actually did read this.

The question has to do with the properties of the Sr mutants. The ones reported on were mutants that had been brought to resistance of 2 mg./cc. and held in culture for several months before study. A further study of this same problem ~~is~~ in about twelve different strains and following their metabolic properties from the time they were selected until they had been cultured for several months showed that the nature of the physiological deviation in the Sr mutants was purely a matter of chance. Some strains were unable to utilize oxygen for increased growth. Others were perfectly capable of this. The ability to use oxygen could be lost in one step or a cell could become resistant and still retain the ability to use oxygen and either retain it throughout the period of study or else lose it at some subsequent date. Throughout all of the strains, however, the one characteristic was that the oxalacetate-pyruvate reaction as we were able to measure it was apparently lost.

With the information that the product of the oxalacetate-pyruvate reaction seems to be a seven-carbon phosphorylated intermediate it was possible to distinguish between two alternatives which had previously arisen. If the resistant and dependent strains had lost the oxalacetate-pyruvate reaction, then they had either acquired the ability to dispense with this compound entirely or acquired the ability to synthesize it by some route which was not sensitive to streptomycin, said route not influencing the same kind of pathway as that from oxalacetate and pyruvate. We, therefore, grew both resistant and dependent strains in considerable quantity in the presence of streptomycin, and found that we were able to isolate the 7-carbon substance from both types and that it was present in apparently one-third the concentration that it occurred in the sensitive strain. To my mind, this means that the substance cannot be dispensed with, but that the resistant strain has "learned" how to make it by a route not inhibited by streptomycin.

With best wishes,

Sincerely yours,

WWU:VMF

Wayne W. Umbreit